PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MJL/VB60395	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/10085	International filing date *(day/month/year)* 28.08.2003	Priority date *(day/month/year)* 30.08.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/22		
Applicant GLAXOSMITHKLINE BIOLOGICALS SA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.03.2004	23.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Noë, V Telephone No. +31 70 340-4181

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10085

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-54 as originally filed

Claims, Numbers

1-34 received on 11.01.2005 with letter of 11.01.2005

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 35,36

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 24 (completely), 25,26 (partially)

   because:

   ☒ the said international application, or the said claims Nos. 24, completely and 25-26, partially (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8,15-21,31,34
	No:	Claims	9-14,22-30,32,33
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	9-34
Industrial applicability (IA)	Yes:	Claims	1-23,27-34
	No:	Claims	

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion (Continuation)

Claims 24-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V. Reasoned statement (Continuation)

1 CITATIONS

Reference is made to the following documents:

D1: JANSEN C ET AL: "Biochemical and biophysical characterization of in vitro folded outer membrane porin PorA of Neisseria meningitidis" BIOCHIMICA ET BIOPHYSICA ACTA. BIOMEMBRANES, AMSTERDAM, NL, vol. 1464, no. 2, 5 April 2000 (2000-04-05), pages 284-298

D2: WO 96/29412 A (BRODEUR BERNARD R ;HAMEL JOSEE (CA); RIOUX CLEMENT (CA); IAF BIO V) 26 September 1996 (1996-09-26)

D3: MOE G R ET AL: "Differences in surface expression of NspA among Neisseria meningitidis group B strains" INFECTION AND IMMUNITY, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, US, vol. 67, no. 11, November 1999 (1999-11), pages 5664-5675

2 NOVELTY (Art. 33(2) PCT)

2.1 D2 discloses recombinant Neisseria meningitidis NspA protein with an electrophoretic mobility of 22 kD, corresponding with the electrophoretic mobility of the refolded NspA protein (see description of the present application page 51, line 30-34). D2 also discloses pharmaceutical compositions comprising this protein for the prevention or treatment of Neisseria infections, antibodies specific for NspA for the treatment, prevention of Neisseria infection and the use of the protein or antibodies for diagnosis (see page 1, line 5-21; page 5, line 24 - page 6, line 9; page 15, line 19 - page 16, line 9; page 21, line 14 - line 33; page 22, line 10 - page 23, line 24; page 31, line 1-

22; examples 4-6,8,12). In view of D2, the subject-matter of claims 9-14, 22-30,32,33 is not considered to be novel.

2.2 D2 also discloses the refolded 22 kD NspA protein in a buffer, which can be considered to be a refolding buffer (see page 43, line 26-31). Since claim 9 does not specify the composition of the refolding buffer (as in claim 1), the subject-matter of this claim is not considered to be novel in view of D2.

2.3 D3 discloses recombinant NspA protein of 22 kD, which is considered to be the electrophoretic mobility of the refolded NspA protein and an antiserum against this protein to treat Neisseria infection. In view of D3, the subject-matter of claims 10,27-30 is not considered to be novel.

2.4 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 9-14,22-30,32 and 33 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

3 INVENTIVE STEP (Art. 33(3) PCT)

3.1 For inventive step analysis of claim 1, D1 is considered to represent the closest prior art and discloses refolding of PorA an outer membrane protein from Neisseria meningitidis. NspA is expressed in E. Coli, cells are disrupted and inclusion bodies comprising the PorA protein are collected and solubilised. PorA is then refolded using a buffer containing the detergent n-dodecyl-N,N-dimethyl-1-ammonio-3-propanesulfonate (SB-12) and ethanolamine. The buffer has a pH of 10.8 and SB-12 is purified over an Al2O3 column. However, It would not be obvious for the person skilled in the art to apply this method to NspA to obtain a refolded NspA protein without any reasonable expectation of success since already refolding conditions for particular PorA proteins are found to be considerably different (see D1). Therefore, claims 1-8 are considered to be inventive.

3.2 Dependent claims 15-21,31 and 34 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, because these features are considered to be obvious

and of general knowledge for the skilled person.